REMARKS

Claims 1-4, 7-16, 18, 19, 39, 40, 44-50 are pending. Non-elected Claims 20-29, 37-39, 41-43 are canceled without prejudice or disclaimer. Above, Claim 1 is amended, without prejudice or disclaimer, and as to the amendment, see, e.g., original claims 5, 6,12; see also Applicants' specification at page 6, lines 26-28. Claims 5-6 are canceled in view of the amendment to claim 1. Claim 40 is amended to correct a misspelled word. As to above new claims 44-50, see the worked examples in Applicants' specification.

In the office action, Claims 1-16, 18, 19, 39 and 40 have been rejected under 35 U.S.C. 112, first paragraph, for alleged non-enablement.

Applicants respond as follows. Without agreeing with the Examiner[1], to advance prosecution, Claim 1 is amended and is substantially, but not exactly, as suggested by the Examiner at the bottom of page 4 of the office action. In the office action (page 4), the Examiner admits that subject matter in which X^2 is halogen or hydroxyl is enabled. First, the Examiner seems to have overlooked parts of the specification in which X^2 is otherwise than halogen or hydroxyl, such as the OMs group shown in Scheme 5 in the specification. Second: "A patent need not teach, and preferably omits, what is well known in the art." MPEP 2164.01. It is well known in the art how to replace a halogen substituent by a nucleofugal group. Reconsideration and withdrawal of the non-enablement rejection are respectfully sought.

In the office action, Claims 1-16, 18, 19, 39 and 40 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Murdock et al. The Examiner admits that "Murdock et al do not teach compounds ... which are drawn to formulae in which the amino containing R group has either a piperidine or pyrrolidine ring in place of the alkylene chain. Further Murdock et al. ... do not teach halo (or other X^2) containing amino groups". The Examiner's theory is that "one skilled in the art of medicinal chemistry would be motivated to make alternate forms of the prior art compound III, by cyclization of the alkylene chains because such structural modifications are routine in the art of design of analogs of known active molecules, further because of the knowledge in

[1] Applicant reserves the right to re-represent, such as in a continuation application, subject matter from original claim 1.

the art that cyclic ring structure, as found in anthraquinone adriamycin are not deleterious for the retention of anti-tumor activity."

Applicants traverse this obviousness rejection.

In Murdock's JMC paper, the focus of heterocyles is mainly on morpholino derivatives, i.e., 12, 13, 48, 49, 57. These are a natural extension of the tertiary ethanolamines described.

None of the Applicants' claimed compounds are morpholino based.

A person of ordinary skill in the art would have lacked motivation to turn away from Murdock's focus on morpholino derivatives.

Besides the morpholino based compounds, Murdock describes one other aliphatic heterocycle (compound 59) i.e., the N-ethylpyrollidine side chain. None of Murdock's compounds are alkoanol substituted heterocycles.

Murdock also describes a heteroaryl (pyridine) derivative (compound 14). This is poorly active in both the *in vivo* test systems and in no way suggests an obvious route to Applicants' compounds.

Also, Murdock's compounds produce negligible median life span increase or zero median life span increase against mouse leukemia and melanoma.[2] In contrast, Applicants' HAQ71 (20 mg/kg) and CAG75 (16 mg/kg) are tested against a resistant xenografted human tumor which is acknowledged to be a much more stringent test of activity than mouse tumors. Both of Applicants' agents produced significant increases in median life span (greater than 166%). See Table 3, page 15 of Applicants' specification. This evidence of record (of unexpected superiority of life span increases for representative embodiments of Applicants' claimed invention contrasted with representative embodiments of Murdock) rebuts the Examiner's contention of obviousness.

Also, Applicants' piperidinyl and pyrollidinyl agents are significantly more active *in vitro* against ovarian cancer cells resistant to cisplatin (A2780/CP70 and A2780/MCP1) than against the parent non-resistant cells (A2780). Applicants' results suggest that the presence of cisplatin-resistance mechanisms in the ovarian cancer cells

[2] Murdock's *in vivo* models use P388 mouse leukemia and mouse B16 melanoma. The N-ethylpyrollidino derivative (compound 59, 200 mg/Kg) produced a negligible median life span increase of 30-40%. The pyridine derivative (compound 14, 250 mg/kg) produces a zero median life span increase.

actually sensitizes them to treatment with Applicants' nonsymmetrically substituted anthraquinones. This result is counterintuitive and very surprising, while, however, also demonstrating a benefit of Applicants' compounds over other agents previously described.

The Examiner further asserts that there is knowledge in the art that a cyclic ring structure as found in adriamycin allows retention of anti-tumor activity. However, the Examiner's reference to adriamycin is not appropriate. A careful comparison of the anthracycline structure, which his dependent on an ether linked aminosugar for activity, with that of the 1,4-disubstituted alkyl amino anthraquinones shows them to be very different. The cyclic groups are not similar, nor are the activities of the compound. It would not be obvious to modify the drug design in the manner suggested by the Examiner. In fact, both the cyclic and the sugar moieties form important subunits of the anthracyclines, which influence the pharmacokinetic and pharmacodynamic properties of this class of agent. As these subunits are not a part of the 1,4-disubstituted anthraquinone molecule such comparison as the Examiner makes is spurious. For example, the fourth ring of adriamycin contributes to the G:C intercalation. Applicants' compounds require the cyclic amino side chain to contribute to DNA stable interactions by H-bonding with DNA-phosphates.

In more detail: The anthracyclines (aminoglycones) including adriamycin owe their activity to their high DNA affinity and associated inhibition of Topoisomerase II (a DNA processing enzyme). This activity is through intercalation of the anthracyline 4-membered ring system between G:C based pairs and stabilization of that interaction via the daunosamine sugar hydrogen bonding with the DNA phosphate backbone. The heterocyclic moiety of the derivatives of the present invention does not contribute to G:C base pair interactions instead stabilizes the binding of Applicants' agents by interaction with DNA phosphates.

For simplicity and brevity we do not comment on each claim, but would like to point out the following regarding claim 9 which was included in the rejection based on Murdock. Murdock has certainly not identified N-oxides at all, let alone as having any activity still less as being cytotoxic.

The inclusion of N-oxides as potential cytotoxics is counterintuitive since the formal charge (N+ -O-) would be repulsive for binding to the DNA phosphate backbone. Hence it would NOT be obvious to include N-oxides of tertiary amines in the compounds disclosed by Murdock, still less in t hose defined by the present claims.

Furthermore, we identify that the N-oxides of these cytotoxic anthraquinones also deactivate the OH, Cl etc. leaving group creating potential prodrugs of agents with BOTH DNA intercalating and alkylating capability.

Applicants' compounds are an entirely new class of agent which have the added advantage that they are converted to cytotoxins with greater activity in resistant tumor cells compared to the non-resistant phenotype.

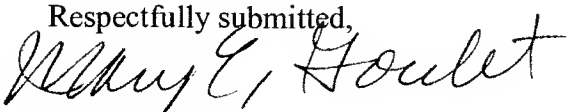
Reconsideration and withdrawal of the obviousness rejection are respectfully sought.

In view of the foregoing, it is respectfully requested that the application be reconsidered, that claims 1-4, 7-16, 18, 19, 39, 40, 44-50 be allowed, and that the application be passed to issue.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at the local telephone number listed below to discuss any other changes deemed necessary in a telephone or personal interview.

A provisional petition is hereby made for any extension of time necessary for the continued pendency during the life of this application. Please charge any fees for such provisional petition and any deficiencies in fees and credit any overpayment of fees to Attorney's Deposit Account No. 50-2041.

Respectfully submitted,



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